

Best of the 2016 AUA Annual Meeting

*Highlights From the 2016 American Urological Association Annual Meeting,
May 6-10, 2016, San Diego, CA*

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KEY WORDS

Inflammation • Microbiome • Prostate cancer • Active surveillance • Disorders of sexual development • Hemorrhagic cystitis • Nephrolithiasis • Four kallikrein assay • Genomic prostate score • OnabotulinumtoxinA • Overactive bladder

More than 2000 posters, abstracts, and videos were presented at the 2016 American Urological Association (AUA) Annual Meeting, held in San Diego, CA, from May 6 to 10, 2016. The editors of *Reviews in Urology* have culled an enormous volume of information from this premier source and present the findings that are most relevant to the practicing urologist.

Focus on Inflammation in Urological Chronic Pelvic Pain

This year saw many excellent sessions presented in the inflammation, infection, and urologic chronic

pain arenas, but clearly the theme this year was the role of inflammation and its interplay with the peripheral and central nervous systems, neurohumoral pathways, and neuromuscular interactions, as well as the urinary tract and bowel microbiome as key etiological factors in patients with urologic chronic pelvic pain syndrome (UCPPS).

For the first time in 2016, a full-day symposium was held on the Human Microbiome in Urologic Health and Disease.¹ During this symposium, Jeremy Burton, in his keynote address, outlined the important role of the microbiome in the urinary tract beyond infection²; David Nelson³ described the complex microbiome of the urinary tract; and Lenore Ackerman⁴ discussed the inflammatory responses to the microbiome in overactive bladder (OAB). Daniel Shoskes⁵ and J. Curtis Nickel⁶ outlined the possible role of the gut and urinary tract microbiota, respectively, in the etiology and pathogenesis of urologic chronic pelvic pain. Our microbiome, which constitutes more microbial cells than we have human cells in our bodies, appears to modulate neural, immunologic, and psychogenic parameters associated with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and interstitial cystitis/bladder pain syndrome (IC/BPS). It appears that it is

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likely not due to a single organism (although as described by Nickel, there is a significantly higher prevalence of fungi (eg, *Candida*) in the urine of IC/BPS patients having flares compared with those not having flares), but rather the diversity and microbial patterns that influence a patient's life experience with these conditions.

The role of the urinary⁷ and bowel⁸ microbiota was further described in the *Prostatitis* poster and podium sessions. Observations that histologic prostate inflammation predicted symptom progression in men with existing CP/CPPS symptoms but not the risk of developing CP/CPPS symptoms in asymptomatic men illustrated that activation of the inflammatory cells likely plays a role in etiology.⁹ The fact that CP/CPPS is associated with periodontal disease,¹⁰ irritable bowel disease,¹¹ and mental disorders¹² further implicates inflammatory pathways in this condition.

The focus of the *Interstitial Cystitis* sessions was also on inflammation and its role in etiology, as well as being the target for therapy. Abstracts demonstrated that interstitial cystitis is associated with increased urine levels of macrophage migration inhibitory factor,¹³ expansion of clonal B cells (particularly in patients with Hunner lesions),¹⁴ expression of specific cytokine patterns,^{15,16} and the role of toxic urinary cations¹⁷ and toll-like receptor activation¹⁸ as either initiator or as part of the inflammatory cascade. Inflammation associated with IC/BPS was shown to be an effective target as a treatment strategy. Oral cyclophosphamide showed some efficacy in treatment-refractory cases¹⁹ that could be predicted by gene expression,²⁰ and lidocaine (which has significant anti-inflammatory properties) delivered via an intravesical device provided

significant relief in patients with Hunner lesion disease, and resolution of the inflammatory Hunner lesion itself.²¹ A novel SH2-containing inositol-5'-phosphatase 1 (SHIP1) activator (which modulates the P13K cellular signaling pathway) was shown to be an exciting potential therapy.²² The mechanism of action of SHIP1 activation was demonstrated in an animal model (cyclophosphamide induced)²³; the pharmacokinetics was shown to be advantageous for a bladder-directed treatment (stable urine concentration at 140-200 times the serum concentration)²⁴; a phase II randomized controlled trial confirmed its efficacy in terms of pain, and urinary and IC/BPS disease-specific symptoms.²²

The emphasis on inflammatory parameters and the microbiome associated with UCPPS was stressed during the Plenary Session by Michel Pontari and J. Curtis Nickel²⁵ as they outlined the scientific progress obtained by the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases Multidisciplinary Approach to the Study of Chronic Pelvic Pain study. The theme of the 2016 annual meeting of the AUA was inflammation and anyone attending the various sessions associated with chronic urologic pain left the meeting with a sense that further developments in this direction will lead to improved understanding and management of UCPPS. ■

[J. Curtis Nickel, MD, FRCSC]

Molecular Imaging of Prostate Cancer

Over the past year we have observed growing interest in molecularly targeted imaging tests for prostate cancer. Among the many targets for prostate cancer imaging, few have received as much

attention as prostate-specific membrane antigen (PSMA), a type II transmembrane glycoprotein that is near ubiquitously overexpressed by prostate cancer epithelial cells.^{26,27} A number of studies evaluating radiotracers targeting this protein were presented. The majority of these abstracts employed the ⁶⁸Ga-PSMA-11 radiotracer (also known as ⁶⁸Ga-PSMA-HBED-CC), a urea-based small molecule that selectively binds to the catalytic site of PSMA. In one study, van Leeuwen and coworkers²⁸ evaluated ⁶⁸Ga-PSMA-11 positron-emission tomography/computed tomography (PET/CT) in patients with biochemical recurrence (BCR) following radical prostatectomy (RP). At enrollment, all patients were believed to be candidates for salvage radiation therapy, with prostate-specific antigen (PSA) values ranging from 0.05 to 0.99 ng/mL. Despite these low PSA values, 38 of 70 (54.3%) patients had at least one identifiable lesion on PSMA-targeted PET/CT. Interestingly, 20 (28.6%) patients had one or more PET-avid lesions outside of the prostate bed. These data demonstrate the sensitivity of this novel imaging test as well as its potential for directing salvage therapy in men with BCR. These same authors also reported data evaluating ⁶⁸Ga-PSMA-11 PET/CT in the preoperative surgical staging of patients with clinically localized disease as defined by conventional imaging.²⁹ In total, 11 of 30 (36.7%) imaged patients were found to have positive lymph nodes at the time of RP. PSMA-targeted PET/CT had a sensitivity of 64% and specificity of 95% for detecting disease-involved lymph nodes. Similar findings were also reported in the presurgical setting by Herlemann and associates.³⁰ Combined, these data suggest a possible role for PSMA-targeted PET/CT to aid in the detection of

lymph-node metastases that are otherwise occult on conventional imaging. This information can potentially be used to steer patients with a positive test result toward a multimodal approach to therapy.

PSMA is not the only target for molecular imaging of prostate cancer. Other radiotracers that have received considerable attention in the literature include ^{11}C -choline and ^{18}F -fluoroethylcholine. Although highly sensitive, these radiotracers offer somewhat more limited specificity, as they are taken up by any cell rapidly undergoing proliferation. Thus, questions remain regarding the performance of choline-based radiotracers relative to PSMA-targeted agents. In one abstract, Albisinni and coworkers³¹ presented data on 17 patients with recurrent prostate cancer who were imaged with both ^{11}C -choline and ^{68}Ga -PSMA-11 PET/CT. In total, 12 of 17 (70.6%) tested positive with both imaging techniques, 4 of 17 (23.5%) tested positive only on PSMA-targeted PET/CT, and 1 (5.9%) tested positive on ^{11}C -choline PET/CT alone. Of particular note, the number of lesions detected per patient was higher with PSMA-PET as compared with ^{11}C -choline, suggesting an overall higher level of sensitivity for PSMA-targeted PET/CT as compared with ^{11}C -choline. These data were echoed in another abstract by Pfister and colleagues³² that compared the diagnostic accuracy of ^{18}F -fluoroethylcholine and ^{68}Ga -PSMA-11 PET/CT. Notwithstanding the limitations of the study's retrospective design, the authors observed a higher level of accuracy with the PSMA-targeted radiotracer.

It is worth noting that other urea-based radiotracers targeting PSMA are also currently under investigation. One such agent, ^{18}F -DCFPyL, was developed at Johns Hopkins University (Baltimore, MD) and

employs ^{18}F as its radionuclide.³³ The use of ^{18}F offers several advantages over ^{68}Ga , including improved spatial resolution due to the emission of lower energy positrons and more favorable dosimetry allowing for higher injectable doses of radiotracer.³⁴ These properties of ^{18}F are believed to result in superior image quality compared with ^{68}Ga . An abstract from our institution (Johns Hopkins University) presented at this year's meeting demonstrated the potential of this radiotracer in patients with an elevated PSA following RP.³⁵ This study found a sensitivity of 65% for detecting sites of disease in patients with PSA values of 0.2 to 1 ng/mL.

We would be remiss if we did not mention that PSMA-targeted imaging also has potential applications beyond prostate cancer imaging. Interestingly, PSMA is overexpressed by endothelial cells within the neovasculature of a number of solid malignancies, including renal cell carcinoma.³⁶ This is in contrast to prostate cancer, in which PSMA is expressed directly on the tumor's epithelial cells. At this year's meeting, two abstracts were presented demonstrating the potential utility of PSMA-targeted PET/CT in patients with the clear cell subtype of renal cell carcinoma.^{37,38} Additionally, we should note that PSMA is not only a target for molecular imaging, but also a promising therapeutic drug target. Batra and coworkers³⁹ presented favorable data from a phase I trial evaluating a therapeutic ^{177}Lu -labeled antibody targeting PSMA in patients with castration-resistant metastatic prostate cancer. Among their findings, the authors observed that 7 of 10 (70%) patients with unfavorable circulating tumor cell counts converted to favorable counts following treatment with this novel form of

radiotherapy in combination with docetaxel.

One additional abstract worth mentioning is the study presented by Bogsrud and associates⁴⁰ that evaluated the PET radiotracer ^{18}F -fluciclovine (also known as ^{18}F -FACBC). ^{18}F -fluciclovine is a synthetic amino acid that is transported into rapidly dividing cells. The presented abstract combined data from three separate studies in which 595 men with biochemically recurrent prostate cancer were imaged with ^{18}F -fluciclovine PET/CT. The authors observed one or more sites of prostate cancer recurrence in 68% of patients and found that the rate of lesion detection corresponded with baseline PSA level. Since the time of presentation at this year's meeting, the US Food and Drug Administration (FDA) has granted approval for this agent in imaging "men with suspected prostate cancer recurrence based on elevated PSA levels following prior treatment," clearing the path for ^{18}F -fluciclovine to become a widely available molecularly targeted imaging agent for prostate cancer. We look forward to seeing additional data generated on this radiotracer and hope to see a comparison with PSMA-targeted imaging. ■

[Michael A. Gorin, MD,
Alan W. Partin, MD, PhD]

Active Surveillance for Prostate Cancer

Active surveillance (AS) was a major theme at the 2016 AUA meeting, with three dedicated sessions. This increased emphasis at the conference reflects the expanding use of AS globally. New data from Sweden showed that, as of 2014, 91% of very low-risk and 74% of low-risk patients nationwide chose AS.⁴¹ Even among men aged < 55 years, 84% and

59% with very low-risk and low-risk disease, respectively, chose AS in 2014. Although older men are more likely to choose AS, data from the University of California-San Francisco showed that men aged < 60 years had a significantly lower risk of grade progression during AS compared with older men (hazard ratio [HR] 0.67, 95% confidence interval [CI], 0.55-0.83).⁴² Thus, they concluded that carefully selected young men are appropriate AS candidates.

Other studies examined different ways to expand eligibility for AS. For example, Kwon and colleagues⁴³ sought to determine whether otherwise low-risk patients with PSA levels > 10 ng/mL could be candidates for AS. They found that men with a PSA level of 10 to 20 ng/mL and histologically favorable disease had similar pathologic outcomes at prostatectomy compared with those with a PSA level < 10 ng/mL; whereas men with a PSA level > 20 ng/mL had a higher risk of upstaging and upgrading. They suggested that surveillance may, therefore, be offered to selected men who are intermediate risk by virtue of PSA but have otherwise favorable biopsy histology.

Another patient population for whom AS has been debated is African American men, who have a higher risk of aggressive prostate cancer. Previous studies reported that African American men with low-risk disease had a higher risk of adverse pathology at prostatectomy.⁴⁴ By contrast, new data from Qi and Mouli⁴⁵ found that African American men were less likely to be diagnosed with low-risk disease upfront, but among those with low-risk disease they had a significantly lower risk of upgrading at prostatectomy. They suggested that African American men with low-risk disease should

be considered eligible candidates for AS.

There has also been controversy regarding the use of AS for patients with perineural invasion on prostate biopsy.⁴⁶ Ahmad and coworkers⁴⁷ examined 600 men on AS in Toronto, Canada, and found that perineural invasion on initial biopsy was not associated with a higher risk of disease progression (HR 1.03; 95% CI, 0.60-1.79). They concluded that the presence of perineural invasion should not be considered an exclusion for AS.

Several prospective AS cohorts have recently reported favorable long-term outcomes for patients with very low- and low-risk disease.^{48,49} New intermediate follow-up data were reported for 639 men on AS at the Cleveland Clinic (Cleveland, OH) from 2002 to 2015.⁵⁰ The cohort composition was 25.0% very low risk, 56.9% low risk, 16.6% intermediate risk, and 1.5% high risk. With a median follow-up of 46.1 months, 36% of the cohort underwent delayed treatment, four men developed metastatic disease, and there were no prostate cancer deaths.

Despite increasing evidence from large cohorts that most men remain on surveillance for more than 5 years, some issues remain with ensuring the appropriate follow-up. Recent studies have suggested that AS in the community may be less “active” than expected.⁵¹ In the Michigan Urologic Surgery Collaborative, Luckenbaugh and coworkers⁵² examined the extent of follow-up testing received by 513 men during a 2-year period on AS. Overall, only 20.2% of the population received at least three PSA measurements and one biopsy, as suggested in the guidelines, with significant variability across practices (9.1%-55.1%; $P < .001$). Future research is needed into the optimal

follow-up protocol and tools to support patients during AS. ■

[Stacy Loeb MD, MSc]

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Pediatric Urology

The Society of Pediatric Urology held its annual meeting in conjunction with the AUA annual meeting. There were three full days of pediatric urology education. Sessions offered a scientific program covering a wide range of topics including voiding dysfunction and enuresis, hypospadias, neuropathic bladder, renal transplant, pediatric tumors, varicocele, and stones. Panel discussion topics included *Disorders of Sexual Development: Evolving Role of Patient Advocacy*, *Prenatal Imaging*, and *Urologic Congenitalism*.

State-of-the-Art Lecture: Fertility for Patients With Disorders of Sexual Development

Thomas F. Kolon presented an excellent overview of fertility in patients with disorders of sexual development (DSD).⁵³ Kolon noted that clinical decision making in patients with DSD is complex, vacillating between tissue preservation to maximize their fertility and gonadectomy due to the risk of tumor development. He discussed 46,XX DSD girls with congenital adrenal hyperplasia (CAH). Although most patients with classic CAH need hormonal supplementation in addition to their cortisol replacement therapy for ovulation, fertility in these patients has been found to be proportional to the severity of the disease. Infertility is observed in patients with simple masculinizing

CAH, but to a lesser degree when compared with those with salt-wasting CAH. In boys with CAH, there is gonadal dysfunction, oligospermia, and precocious puberty—thought to be due to high concentrations of adrenal androgens—which can lead to hypogonadotropic hypogonadism. It follows that paternity in this group is markedly decreased when compared with healthy control subjects.

Patients with 45,X/46,XY who are raised as males pose other concerns. The intra-abdominal gonad has a risk of malignancy including gonadoblastoma/dysgerminoma. Kolon reviewed the results of a study by Martinierie and colleagues⁵⁴ examining puberty and fertility in 20 patients with 45,X/46,XY. Puberty was spontaneous in 17, whereas 6 boys needed testosterone to complete puberty. Almost half of the patients had signs of declining testicular function at the end of puberty, with increased levels of follicle-stimulating hormone, and low levels of testosterone and/or inhibin B. In addition, an abnormal structure of the Y chromosome, which is known to alter fertility, was identified in 10 of 16 patients.

The ovotesticular DSD patients (those with 46,XX, 46,XY, and 46,XX/46,XY) are complex due to their varied gonadal status—ovary (O), testis (T), or ovotestis (OT).^{53,55} The gonadal makeup of OT/O is seen in 34%, OT/OT in 29%, and O/T in 25%. Almost 90% of OT has a “mixed” histology composed of ovarian tissue around a core containing stroma and both intermingled ovarian and testicular tissue. In approximately half of these gonads, the testicular tissue is compartmentalized in the lower pole as a core with ovarian tissue surrounding it, which is thicker in the upper pole. The finding of mixed gonads was independent of karyotype—46,XX or 46,XY. The

remainder (11%) is bipolar with an irregular interdigitating junction between the ovarian and testicular components. Histologic examination of the testes shows only a few normal germ cells with rare spermatozoa. There is hyalinization of seminiferous tubules, Sertoli cell only, interstitial fibrosis, and Leydig cell hyperplasia. In considering testicular tissue preservation, one must not overlook the possible development of a gonadoblastoma/dysgerminoma in XY intra-abdominal gonads, especially because fertility has been reported in only one man. Ovaries, however, have numerous primordial follicles in various developmental stages, which parallel the clinical findings of breast development, cyclic menses, and ovulation. In summary, the gonad that is contrary to the sex of rearing is removed. Despite this and histologic observations, fertility has remained surprisingly rare, with only three cases in women reported.

Clinical Abstract Finalists: Interpretations of Pediatric Urodynamic Tracings

The investigators from Vanderbilt University (Nashville, TN) investigated the interobserver reliability in interpreting pediatric urodynamic studies of patients with neurogenic bladder, because evidence suggests poor agreement among physicians.⁵⁶ They developed an anonymous electronic survey consisting of 20 clinical histories of patients treated between 2014 and 2015, which included a urodynamic tracing and a fluoroscopic image. Six faculty members completed the 20 scenarios examining variables including bladder capacity, compliance, and end-filling detrusor pressure. Comparisons were made among the responses and the clinical key or original interpretations and treatment recommendations

given in the patient's medical record. Moderate agreement was found when comparing the clinical key with faculty responses (κ 0.5-0.66; $P < .038$). A range of agreement was observed when the responses to each of the scenarios were examined individually. They found a strong correlation between raters ($r_s > 0.6$) when they examined the bladder neck and shape on fluoroscopy, decisions to alter treatment, and assessment of bladder safety. Clinical decision making was driven by bladder pressure, bladder shape on fluoroscopy, and filling curve shapes.

Germ Cells in Gonads of Patients With DSD

Investigators from Children's Hospital of Chicago examined histologic slides of gonads of patients with DSD over the past 12 years.⁵⁷ The pathologic classification of the gonad, composition of the stroma and quantification of germ cells were determined. They hypothesized that if germ cells were present, fertility may be possible.

Germ cells were identified in 30 of 44 specimens (68%) with a median age of 34 months at surgery. The presence of germ cells varied by diagnosis with complete androgen insensitivity, mixed gonadal dysgenesis, and ovotesticular DSD having the most potential for finding germ cells in the specimens. Also, the presence of germ cells was found to be age dependent, with a decrease in germ cells being found in the 4- to 11-year-old specimens. The authors concluded that fertility potential exists in patients previously thought to be infertile.

Childhood Cancer Risk of Siblings and Cousins of Men With Poor Semen Quality

Researchers from Salt Lake City, UT, studied the relationship of poor semen quality and childhood cancer

risk of siblings and cousins because infertility and cancer are increasingly thought to be associated.⁵⁸ They performed a retrospective cohort study using subfertile men who participate in their assisted reproductive health study and fertile control subjects from the Utah Population Data Base from 1994 and 2011. All relatives of these patients and control subjects are linked to their semen analysis study base.

The study consisted of 12,889 men with complete semen analysis and a similar number of fertile controls with 79,750 siblings and 435,318 cousins; 210 childhood cancers were identified in the siblings and 1183 were identified in cousins. Siblings most commonly had acute lymphocytic leukemia (ALL; 44/210), brain cancer (37/210), and Hodgkin lymphoma (18/210), whereas the cousins most commonly developed ALL (223/1183), brain cancer (176/1183), and bone/joint cancer (99/1183). Oligozoospermia increased the risk of any childhood cancer in siblings by twofold, whereas ALL was increased threefold in siblings when compared with fertile control subjects. This association with semen parameters was not found in the cousins of men with infertility. ■

[Ellen Shapiro, MD, FACS, FAAP]

Hemorrhagic Radiation Cystitis: Natural History, Current Treatment, and Future Development

Radiation therapy (RT) of the pelvis is the most common etiology of noninfectious hemorrhagic cystitis. Although the condition is rare, the complication is severe. Current treatment options are inadequate due to poor treatment response and high recurrence rates.

Palou and associates⁵⁹ presented a large series of patients from 1986 to 2014 with radiation cystitis entitled “Natural history and predictive factors for hospitalization in patients with radiation cystitis. Results from a large retrospective study.” This was an observational retrospective study in 156 patients and main outcomes assessed were presence of hematuria, number of emergency room visits, and hospital admissions. The authors reported that the mean age at diagnosis of radiation cystitis was 68 years and 93% were men. Indications for RT included 90% for prostate cancer, 6% for gynecologic cancer, 2% for bladder cancer, 1% for rectal cancer, and 1% for other malignancies.

Mean time from RT to diagnosis of radiation cystitis was 7 years and 76% had at least one episode of gross hematuria. Mean number of emergency room and hospital admissions was four and four, respectively. Mean follow-up after diagnosis was 86 months and, eventually, 7% of patients needed a cystectomy. During the follow-up period, 23% died, approximately half from their cancer and half from other causes. The authors concluded that hematuria is the most common presenting symptom of radiation cystitis. They noted that a previous history of RT for prostate cancer significantly increases the risk of hematuria, risk of emergency room visit, and hospitalization.

Bassett and associates⁶⁰ presented on the surgical outcome of urinary diversion for complications of RT for prostate cancer entitled “Urinary diversion for complications of radiation therapy for the treatment of prostate cancer: updated results from the Trauma and Urologic Research Network of Surgeons.” The authors evaluated men who underwent conduit or continent catheterizable pouch

urinary diversion due to complications following RT from prostate cancer from the Trauma and Urologic Research Network of Surgeons from 2007 to 2015 at nine sites. They found 71 men who met inclusion criteria and the mean age was 71 years; 56% of patients had combined-modality therapy (prostatectomy with adjuvant radiation or combinations of radiation).

The median duration from radiation to urinary diversion was 8 years. The mean number of operations for radiation-associated complications prior to diversion was four; 17% of men underwent a continent catheterizable pouch and 83% underwent urinary conduit. Overall complication rate was 68% within 3 months.

There was no association between perioperative complications and type of radiation, combined modality therapy, comorbidity, or prior number of urologic procedures. Men with a lower body mass index developed more serious complications than their overweight counterparts. Complications requiring surgical intervention occurred in 21% of men that pre- or perioperative characteristics did not predict.

The authors concluded that urinary diversion in prostate cancer survivors with prior RT exposure has a high rate of complications. They found no association between complications and type or amount of radiation, age, type of diversion, or time to diversion. An unexpected observation was that the rate of complications was decreased in overweight men. One hypothesis is that these men may have had more nutritional reserve.

Zwaans and colleagues⁶¹ presented preclinical novel therapy for the treatment of hemorrhagic radiation cystitis entitled “Intravesical instillation of liposomal-tacrolimus (LP-10) is an effective treatment for chronic radiation cystitis.” They

developed a CT-guided three-beam radiation technique delivered specifically to the urinary bladder using a Small Animal Radiation Research Platform. Weekly micturition patterns were measured and mice were tested for the development of hematuria. After 20 weeks, the bladders were instilled with saline, liposomes, or liposomal tacrolimus. Mice were sacrificed after 25 weeks.

The mice tolerated bladder irradiation without systemic toxicity. Intravesical instillation of tacrolimus did not alter leukocyte count after instillation. Bladder radiation resulted in immune infiltration, damaged blood vessels, collagen deposition, edema, and thinning of the urothelial wall. Treatment with liposomal tacrolimus significantly improved radiation-induced damage without side effect.

The authors developed a chronic mouse radiation cystitis model that closely mimics the human condition and intravesical instillation of liposomal tacrolimus prevents adverse systemic effects and may be a promising treatment for patients suffering from hemorrhagic radiation cystitis.

In summary, there was rising interest in hemorrhagic cystitis due to radiation therapy. Although the condition is rare, the complication is severe and current treatment options are inadequate. Novel therapies are being developed that offer new hope. ■

[Michael B. Chancellor, MD]

Dr. Chancellor is the founder and Chief Scientific Officer of Lipella Pharmaceuticals, Inc. (Pittsburgh, PA).

Endourology and Nephrolithiasis

There were a number of interesting presentations related to endourology and nephrolithiasis delivered at

the 2016 AUA meeting. I highlight papers related to the pathophysiology of nephrolithiasis, epidemiology, patient evaluation, stone prevention, and surgical stone removal.

There is compelling evidence that Randall plaque plays a role in stone formation, resulting in calcium oxalate calculi stone formation in many patients. In addition, inflammation has also been implicated in stone formation. There were presentations that provided information on these areas. Taguchi and associates⁶² demonstrated genes related to oxidative stress and proinflammatory states were expressed to a significantly higher extent in calcium oxalate stone formers than normal renal papillary tissue. Chen and colleagues⁶³ found that Randall plaque contains osteopontin and osteocalcin and noted that the former protein was in close proximity to vascular structures. Whether these proteins play an active or passive role in the generation of Randall plaque needs to be determined. Okada and associates⁶⁴ performed a proteomic analysis of the urine and blood of calcium oxalate stone formers and normal subjects. They found lower levels of urinary proteins associated with activation of M2 macrophages (anti-inflammatory macrophages) in stone formers as well as reduced function of these macrophages. This same group⁶⁵ demonstrated that M1 macrophages (inflammatory) stimulated renal calcium oxalate crystal deposition and M2 macrophages limited such crystal formation in a murine model of hyperoxaluria. Dominguez Gutierrez and colleagues⁶⁶ reported that monocytes exposed to calcium oxalate crystals produced cytokines and chemokines known to stimulate macrophage ingestion of these crystals. This response was not demonstrated with hydroxyapatite crystals.

Stone patients with short gut syndrome or ileostomies may have ducts of Bellini that are plugged with calcium phosphate, which is not predicted based on the acidic urine typically present in this cohort. Borofsky and associates⁶⁷ measured pH in the ducts of Bellini of these patients and found that pH was significantly higher than that of bladder urine. This provides a plausible explanation for why calcium phosphate plugs develop in stone formers with acidic urine. This could be due to focal renal tubular injury inducing renal acidification defects. A search for the inciting event is warranted.

Reduction in fat consumption has been recommended for patients subjected to malabsorptive bariatric surgery who develop hyperoxaluria, as it may reduce gastrointestinal oxalate absorption. Canales and Hatch⁶⁸ demonstrated in a rat gastric bypass model that high fat consumption augments oxalate absorption, but they also found this to be true in animals without bypass. The translational message is that reduction in fat consumption may benefit those with idiopathic hyperoxaluria.

The occurrence of stone events with warm climate is well established. Tasian and colleagues confirmed this using patient data from South Carolina and also reported that this was influenced by age.⁶⁹ This was true for those aged 20 to 65 years but not for those younger, in whom stone manifestation occurred more commonly during periods of lower temperature ($< 0^{\circ}\text{C}$).

Stone disease imparts a significant economic burden in the United States. Tasian and associates⁷⁰ reported that this burden is increasing. They demonstrated that the costs for inpatient, emergency, and surgical care has nearly doubled from 2001 to 2012 in South

Carolina—a definite economic ouch! Cone and colleagues⁷¹ demonstrated that a disproportionate amount of inpatient economic resources are consumed in caring for patients older than age 65 years based on an Agency for Healthcare Research and Quality Nationwide Inpatient Sample (NIS).

Ultrasonography has been proposed as a reliable method of evaluating patients with suspected renal colic. However, it does have limitations, which were illustrated in a multi-institutional, retrospective study presented by Larson and associates.⁷² They found that it was less sensitive and frequently overestimated stone size. This limits the clinician in providing clear directives for patient management.

Patients with renal colic are typically evaluated in an emergency room. Luckenbaugh and colleagues⁷³ reported that almost 50% of these individuals do receive follow-up care, particularly those who are young, unemployed, and reside in rural areas. Although a number of these patients have probably passed their stones spontaneously, some are undoubtedly at risk for renal damage from obstruction, returns to the emergency room, and recurrent stone events that could be prevented with appropriate follow-up evaluation.

Twenty-four-hour urine testing is endorsed for the management of patients with recurrent stones and those first time stone formers that are at high risk for recurrence. Patients find these collections inconvenient, especially if asked to undertake this during vocational activities. Hinck and associates⁷⁴ reported that the supersaturation of calcium oxalate from a 12-hour nighttime collection significantly correlated with that of a 24-hour collection. Further and more expanded studies are needed to confirm whether such a

truncated collection period would be adequate/accurate in defining urinary stone risk parameters.

The utility of medical expulsive therapy has recently been questioned. Medical expulsive therapy has been based on the oral intake of medications, which are known to relax smooth muscle. Streeter and colleagues⁷⁵ investigated a new approach: periureteral injection of botulinum toxin A in a porcine model. They reported that it facilitated stone passage. The cost and invasiveness of this approach may limit its utilization in humans.

Hyperoxaluria is a known risk factor for the formation of calcium oxalate stones. The common approaches for reducing oxalate excretion have been reduction of dietary oxalate and maintenance of normal calcium intake. Grujic and associates⁷⁶ reported that the administration of an oxalate-degrading enzyme to swine on a high-oxalate diet significantly reduced oxalate excretion. Clinical trials are warranted to test the efficacy of this agent in humans. Patients with type 1 primary hyperoxaluria develop stones, nephrocalcinosis and are at high risk for chronic kidney disease and end-stage renal disease. Lai and associates⁷⁷ demonstrated that the administration of supplemental alanine in a Chinese hamster ovary cell model of primary hyperoxaluria type 1 reduced the generation of oxalate and improved cell viability. This could be a future therapy for this cohort.

Ureteroscopy is now the most commonly used technique for stone removal in North America and many other parts of the world, supplanting shock wave lithotripsy. Prior studies have demonstrated that the utilization of percutaneous nephrolithotomy (PCNL) has been stable. However, using an NIS, Stern and associates⁷⁸ found

that the utilization of PCNL from 1998 to 2011 has doubled. I anticipate that this trend will change based on the utilization of ureteroscopy for larger renal stones that has been popularized over the past 5 years. PCNL still provides the patient with the best chance of being rendered stone free with a single procedure. The term *clinically insignificant fragment* continues to be used after stone-removing procedures. Olvera-Posada and colleagues⁷⁹ have demonstrated that this is a misnomer for PCNL. They reported that the majority of 44 patients with residual fragments after PCNL documented on a post-operative CT scan required another intervention over a near 5-year follow-up.

The delivery of shock waves at a slower rate has been demonstrated to improve stone-free rates in humans. Slower shock wave delivery using a Dornier HM3 lithotripter (Dornier MedTech, Weßling, Germany) in a porcine model was previously shown to limit histologic evidence of renal damage in a porcine model. Connors and associates⁸⁰ demonstrated that this did not attenuate renal injury in a similar model using a Dornier Compact S lithotripter, at 60 versus 120 shocks per minute, for 2500 total shocks.

There were a number of papers that profiled the current status of ureteroscopic stone removal. Chew and associates⁸¹ reported a multicenter experience comparing the techniques of laser dusting of 5- to 20-mm renal stones, and laser fragmentation and basket removal of generated fragments; stone-free rates with the latter were significantly greater, 86.3% versus 59.2%. Ingimarsson and colleagues⁸² reported that bilateral ureteroscopic stone removal could be effectively done with minimal morbidity. Morhardt and associates⁸³

demonstrated that the level of the injury influenced the results of ureteroscopic stone removal in those with spinal cord injury; morbidity increased and stone-free rates were lower with higher levels of injury. Ureteral stricture is a recognized complication of ureteroscopic stone removal. May and colleagues⁸⁴ reported a 3% risk of this complication based on national US database of insured patients. Ahmed and associates⁸⁵ found that the administration of tamsulosin 1 week prior to an attempt at ureteroscopic ureteral stone removal using a semi-rigid instrument facilitated scope passage and resulted in a higher stone-free rate. The costs of ureteroscopic stone removal are influenced by many variables, including the length of the procedure, utilization of disposables, and maintenance of the endoscope. Borofsky and colleagues⁸⁶ reported that the latter might be substantial for flexible ureteroscopes, particularly digital devices (approx. \$1200 per case). These data were generated from a high-volume center of excellence. A disposable digital ureteroscope is now on the market. Cost modeling and comparisons of effectiveness with nondisposable scopes are needed to define whether utilization of this technology should be used at one's institution.

The work profiled in this review reveal steady progress in defining mechanisms of stone formation, epidemiologic trends, methods of preventing this disease, and the optimization of stone removal. ■

[Dean G. Assimos, MD]

Prostate Prognostic Markers

In no other common malignancy does the central conundrum that rules prostate cancer exist—the relative minority of cancers with significant malignant potential that

exist among men who harbor the disease. Significant advances in the development of novel markers that can aid clinicians in differentiating these two forms of cancer (and thus optimize treatment recommendations) have been realized.

Andriole and colleagues⁸⁷ capitalized on the extensive Prostate, Lung, Colorectal and Ovarian database to evaluate the four kallikrein (4K) assay developed by OPKO Health (Miami, FL) in an effort to enhance detection of high-grade cancer. They added an additional analyte (microseminoprotein-beta [MSP]); 946 men were evaluated, including 113 African Americans. Importantly, a prespecified model was utilized. The area under the curve (AUC) for detection of high-grade cancer was significantly greater with the 4K score than for age and PSA alone (0.79 [95% CI, 0.75-0.82] compared with an AUC of 0.69 [95% CI, 0.64-0.74]). A non-significant enhancement in identification of risk was observed in African American men. Adding MSP to the model very slightly increased the AUC from 0.79 to 0.81. The central question remains, does the impressive specificity afforded by this test offset the risk of not performing biopsy in some men with high-risk disease that will occur when the sensitivity remains well below 100%?

Van Neste and associates⁸⁸ validated a novel urine-based prostate cancer biomarker. They studied two genes' (*HOXC6* and *DLX1*) mRNA combined with standard clinical risk factors to identify men with high-grade (Gleason score > 6) disease; 519 men were evaluated in a training cohort and validation was done in specimens from 386 men. The mRNA assay worked in whole urine samples and proved to be a good predictor for the detection of high-grade prostate cancer with an AUC of 0.74 (95% CI, 0.70-0.78).

The multimodal approach reached an AUC of 0.88 (95% CI, 0.85-0.91) for men with high-grade prostate cancer, with the mRNA assay, PSA density, and digital rectal examination. This mRNA-based approach was significantly better in identifying high-grade prostate cancer patients compared with PCA3 (AUC: 0.68; $P < .001$) and the prostate cancer prevention trial risk calculator (AUC: 0.77; $P < .001$). These impressive results need further validation and again the acceptance of missing some men with high-risk disease that have lower levels of these markers must be demonstrated in utility trials.

Bishoff and coworkers⁸⁹ demonstrated that the Cell Cycle Progression Score (CCP; Myriad Genetics, Salt Lake City, UT) provides significant prognostic value on biopsy material in men with a Gleason score < 7. Previously, a multitude of validation studies have demonstrated that CCP provides the best assessment of eventual oncologic progression in all risk groups. A meta-analysis of 204 men initially managed conservatively and 236 treated with RP who had low-grade disease was performed. Outcome was either prostate cancer death (in conservatively managed cohorts) or BCR (in post-RP cohorts), and association with outcomes was evaluated by Cox proportional hazards survival analysis and likelihood ratio tests. The cell cycle progression signature was a significant predictor of outcome in the meta-analysis. In univariate analysis, both CCP and combined clinical risk (a prognostic model combining CCP and cancer of the prostate risk assessment [CAPRA]) were significant predictors of outcome (HR 1.50; $P = .0099$ and HR 1.83; $P = .0014$). CCP remained significant after adjusting for CAPRA (HR 1.46; $P = .019$) or after adjusting for a de novo multivariable

model, including PSA, clinical stage, percent of positive cores, and age at diagnosis (HR = 1.47; $P = .017$). This study adds to the evidence that CCP score provides significant prognostic discrimination in all risk groups of men with clinically localized disease.

The risk of disease-specific mortality (DSM) after definitive treatment remains a critical factor in selecting therapy. Karnes and colleagues⁹⁰ evaluated a 22 genomic classifier (GC) to assess men who had high-risk disease after RP to assess DSM. Subjects had pathologic pT3N0/N1, positive margins, or RP Gleason score ≥ 7 , and were followed for at least 10 years. A total of 511 men were evaluated and 110 had DSM (22%). High GC score increased DSM risk nearly fourfold (HR 3.87; $P < .0001$), and increased the AUC from 0.767 to 0.804. Although these data are compelling, the utility would obviously be far greater if these results can be reproduced on biopsy material.

Ross and associates⁹¹ evaluated the *PTEN/ERG* status in men with favorable risk prostate cancer (Gleason Score 3+3). *PTEN* and *ERG* status was assessed immunohistochemically on the diagnostic biopsy tissue. Loss of *PTEN* was defined by marked decrease in or complete loss of staining across $> 10\%$ of tumor cells. A tumor was considered *ERG* positive if any tumor glands showed nuclear *ERG* expression. Among 158 cases, *PTEN* loss was detected in 13 (8%) men. Subjects with and without *PTEN* loss did not significantly differ in age, race, clinical stage, or median PSA (all $P > .05$), whereas those with *PTEN* loss had a higher number of positive cores (median 4.5 vs 2; $P < .001$) and maximum percent core involvement (50% vs 15%; $P = .03$), and showed a trend toward less frequent National Comprehensive Cancer Network

(NCCN) very low-risk classification (20% vs 46%; $P = .10$). The cohort with *PTEN* loss was significantly more likely to undergo RP (40% vs 14%; $P = .03$). All five men (100%) with *PTEN* loss had upgrading or non-organ-confined disease compared with 57% of men with *PTEN* intact. *ERG* was expressed in 46% of the overall cohort and did not correlate with outcome at RP. The authors wisely concluded that, although rare, loss of *PTEN* is associated with GS upgrading or non-organ-confined disease at surgery, and men with *PTEN* loss should strongly consider early definitive treatment. However, as unfavorable pathology was also common in men with normal, this feature should not be used to encourage conservative management strategies.

The controversy surrounding *PTEN* continues. Magi-Galluzzi and associates⁹² examined a 17-gene genomic prostate score (GPS; Genomic Health, Redwood City, CA) in conjunction with tests for *PTEN* loss among 441 men undergoing RP in all risk groups; 38% vs 25% had loss of *PTEN*, depending on the methodology employed (fluorescence in situ hybridization [FISH] or immunohistochemistry [IHC]). Although *PTEN* status by FISH or IHC was associated with BCR ($P < 0.001$) and clinical recurrence ($P < .05$) in univariate analysis, after adjusting for GPS, neither FISH nor IHC *PTEN* was a significant predictor of either BCR ($P > .05$) or clinical recurrence ($P > .1$). GPS remained very strongly associated with clinical and BCR after adjusting for *PTEN* (HR/20 units = CR 4.0 [95% CI, 2.1-7.6], BCR 2.1 [95% CI, 1.3-3.3] by FISH; HR/20 units = CR 4.0 [2.3, 6.7], BCR 1.6 [95% CI, 1.1-2.3] by IHC). If reproduced, and particularly if they can be validated in biopsy material, these data raise

questions of the significance of *PTEN* in patients being evaluated with modern molecular prognostic assays.

In the 1970s there was great interest in prostate cancer cytology (based on needle aspiration) for prostate cancer diagnoses. It was supplanted after the pioneering work of Gleason demonstrated that the architecture of prostate cancer histology provided very significant prognostic information. History was reassessed in the report from Gawlik and coworkers,⁹³ who utilized computer image analysis of Feulgen and hematoxylin-eosin (H&E) nuclear features to predict BCR in men following RP; 69 patients (20 BCR and 49 nonrecurrences) were assessed with mean BCR-free survival time of 6.6 years and follow-up to 14 years. A total of 242 quantitative histomorphometric (QH) features describing nuclear shape, architecture, and disorder were calculated from the H&E and Feulgen-stained tissue microarray core images in each patient. The top 10 ranked features for each stain type were selected.

Gleason score did not discriminate between those who did or did not have BCR predictions using QH features extracted from Feulgen and H&E images and revealed statistically different outcomes. Combining Gleason score, H&E, and Feulgen together showed the highest classification accuracy (0.75; $P < .001$). Although this is a very small study, if validated, this may provide a fruitful arena for development—perhaps there is something new (again) under the sun.

Taverna and colleagues⁹⁴ have taught us again that great discoveries may not require millions of dollars in laboratory equipment. They evaluated whether highly trained dogs could detect BCR following RP by smelling patient urine.

A total of 114 consecutive men with clinical localized prostate cancer were investigated (follow-up mean: 28 mo; median: 28 mo; range 19-37 mo). Two dogs were trained to sit when they detected prostate cancer-specific volatile organic compounds (VOCs) in the urine samples. In preoperative specimens, both dogs were able to detect prostate cancer-specific VOCs in the urine samples of men with prostate cancer with 100% accuracy; 45 days after RP neither dog detected prostate cancer-specific VOCs in the urine samples of the 104 men with a serum PSA level < 0.01 ng/mL. Both dogs detected prostate cancer-specific VOCs in samples collected from two of six men with PSA levels > 0.01 ng/mL and < 0.2 ng/mL, and both dogs were able to detect VOCs in the samples each of the four men with PSA levels > 1 ng/mL (ie, persistent disease). During the successive follow-up, 9 of 110 patients (8.1%) had BCR. Both dogs were able to detect prostate cancer VOCs in the urine samples of seven of these nine patients (77.7%). These findings are impressive. Now the investigators should utilize that expensive laboratory equipment to delineate the relevant VOCs.

Gleicher and associates⁹⁵ evaluated the *BRCA2* gene (first identified as one of the genes responsible for hereditary breast and ovarian cancer risk) in men with prostate cancer by conducting a literature meta-analysis. Previously, it had been established that approximately 1.2% of prostate cancer cases occur in patients who carry mutations for the *BRCA2* gene and these patients often have more aggressive prostate cancer with higher rates of cancer-specific mortality. A systematic review was performed utilizing the MEDLINE database aimed at capturing clinicopathologic characteristics and outcomes

of men with *BRCA2*+ associated prostate cancer. The meta-analysis was performed on outcomes data from included studies; 12 publications met inclusion criteria representing a total of 261 *BRCA2*+ men. The mean age for *BRCA2*+ carriers was 61.7 years and mean PSA level was 19.6 ng/mL; 71% of *BRCA*+ prostate cancer cases presented with at least a Gleason score of 7, 41% with T3/T4 disease, and 26% with M1 disease. Survival was worse in *BRCA2*+ carriers with overall survival HR 3.3 (1.56-6.95) and cancer-specific survival HR 3.0 (2.2-4.1 *BRCA2*+ carriers had significantly higher rates of metastatic disease [17.4%] vs the general population [4.4%], as well as higher rates of T3/T4 disease [40.3% in *BRCA2*+ vs 10.8% in the Surveillance, Epidemiology, and End Results Program]). These findings are certainly compelling and prospective *BRCA* testing in contemporary prostate cancer patients is warranted. In a related matter, recent changes in NCCN guidelines for hereditary cancer testing have echoed these finding and recommend *BRCA* testing in men with Gleason 7 or higher prostate cancer who have a significant family history of prostate, breast, ovarian, or pancreatic cancer to provide potential hereditary cancer risk information to their family members. ■

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Female Urology/ Incontinence and Urodynamics

This year's AUA meeting section on Female Urology/Incontinence and Urodynamics was packed with amazing presentations. The section included over 350 abstracts, Plenary

Sessions, Second Options Cases presented on chronic pelvic pain in women, nocturia, and mixed incontinence, and an international perspective on vaginal mesh for stress urinary incontinence. The section also included 14 well-attended courses indicating the interest and enthusiasm the AUA attendees have for Female Urology/Incontinence and Urodynamics.

The Society of Urodynamics Female Pelvic Medicine and Urogenital Reconstruction (SUFU) held a half-day meeting at the start of the AUA. Program Chair Michael Kennelly built a program around the central theme of neurourology. The afternoon featured lectures by Alan Wein⁹⁶ and Christopher Chapple⁹⁷ on detrusor underactivity. The SUFU meeting also included lectures, panels, and debates on topics such as the management of incontinence in patients with spinal cord injury, treatment of detrusor external sphincter dys-synergia, and special consideration in neurologic disorders. One of the lectures by John Stoffel⁹⁸ on comparative effectiveness of bladder management strategies highlighted a theme for the afternoon program—the need to standardize. By standardizing terminology, measures, and outcomes, we will be able to more effectively compare management options in the future.

At the SUFU meeting the much-anticipated OAB clinical care pathway was launched. Urology practices have independently started to use various care pathways to improve outcomes, enhance the patient experience, increase access to therapies, and improve efficiency. This SUFU clinical care pathway for OAB is meant to be a comprehensive, evidence-, and expert opinion-based pathway that all practices can use. The document is easy to follow, and helps people understand the treatment

paradigm in a practical manor. The carefully crafted document can be used as a handout helping with patient education. The document is detailed enough that it would also be a great tool to educate allied health care professionals about when to consult OAB experts in the community. The document can be found at <http://sufuorg.com>. The clinical care pathway also developed a patient-friendly “roadmap,” complementing the SUFU clinical care pathway in a format and language geared directly at patients.

Two anticipated studies that focused on OAB therapies were presented. The first was titled “Improved patient-reported outcomes (PROs) with mirabegron add-on treatment in a randomized, double-blind, phase 3b study in incontinent overactive bladder (OAB) patients with an inadequate response to solifenacin.”⁹⁹ In this study, patients who remained incontinent after a 5-mg run-in of solifenacin were randomized to combination therapy (solifenacin 5 mg + mirabegron 25 mg increasing to 50 mg), solifenacin, 5 mg and solifenacin, 10 mg. Combination therapy outperformed both doses of solifenacin as monotherapy in health-related quality-of-life measures and treatment satisfaction.

The other highly anticipated trial that was presented was “Sacral neuromodulation vs onabotulinumtoxinA for refractory overactive bladder.”¹⁰⁰ The study was carried out in a population of OAB patients considered to be severe. The patients were randomized to sacral neuromodulation and onabotulinumtoxinA (200U [the FDA-approved dose of OnabotulinumtoxinA for idiopathic OAB is 100U]). At the 6-month endpoint, onabotulinumtoxinA outperformed sacral neuromodulation in reduction of urgency urinary incontinence episodes

per day, the primary endpoint of the study. OnabotulinumtoxinA achieved complete resolution of urgency urinary incontinence in 20% of patients versus 4% for sacral neuromodulation ($P < .0001$). Patients in the onabotulinumtoxinA group had the need for transient catheterization at a rate of 16% at 2 weeks, 8% at 1 month, and 2% at 6 months. Devised revision/removal was 3% at 6 months in the sacral neuromodulation group.

There was also exciting work presented on nocturia, a common condition with significant quality-of-life implications. One abstract worth highlighting was entitled “Eat right and wake up less? Exploring the link between socioeconomic and dietary factors and nocturia.”¹⁰¹ The authors looked at the National Health and Nutrition Examination Survey and found that family income, as manifested by grocery spending and dietary quality is a robust predictor of nocturia. These findings highlight that common disease states can have a significantly different burden in different populations. The authors call for health policy changes to propagate the need of prevention by simply providing access to cheaper, higher-quality foods.

Another presentation on the topic of nocturia was a new nasal formulation of low-dose desmopressin, SER120.¹⁰² The subjects in the study were a very diverse group that had two or more voids per night that interrupted sleep. The advantage of using such a mixed group is that the findings are more easily generalized to the symptom complaint (nocturia) rather than a unique patient group. The trial first showed the safety of this formulation with only 0.76% of patients in the 1.5 µg group and no patients in the 0.75 µg group having hyponatremia (defined as serum sodium < 125 mmol/L or < 130 mmol/L

with symptoms). The improvement in number of nighttime voids proved to be significant compared with the placebo-control group.

The section also included the topic of pelvic organ prolapse, another prevalent condition affecting many of our female patients. Khan and colleagues¹⁰³ utilized Medicare data to look at long-term outcomes of the different routes of apical prolapse repair. In this “apex only” prolapse group, prolapse reoperation rates (at 10 y) were 20.7% for women who had a vaginal repair compared with 7.9% for women with an abdominal repair ($P = .003$). This does seem to match numbers from other clinical research but the data set has some limitations, including lack of severity assessment and lack of rationale for specific procedures.

Other interesting work was presented titled “Outcomes of minimally invasive abdominal sacrocolpopexy with resident operative involvement.”¹⁰⁴ The findings and topic are of the utmost importance as we try to train a shrinking pool of urologists to treat an aging population of patients. The authors used the National Surgical Quality Improvement Program® (American College of Surgeons, Chicago, IL) database for patients undergoing laparoscopic or robotic sacrocolpopexy for pelvic organ prolapse from 2006 to 2012 to understand the impact of resident involvement. They showed that operating room participation of a resident late in training (postgraduate year > 4) in minimally invasive sacrocolpopexy, resulted in a longer operating room time. This was not the case for residents in postgraduate years 1 to 3. Length of stay and all 30-day perioperative outcomes are not affected by resident involvement.

There were numerous presentations on urodynamics. One worth

highlighting describes a novel technique using ultrasound imaging during urodynamics to assess for detrusor wall tension and stress. Nagle and associates¹⁰⁵ presented “Addition of ultrasound bladder imaging during urodynamics to calculate detrusor wall tension and stress.” With the added data obtained from ultrasound they describe calculating wall tension as vesical pressure \times luminal area, wall stress as wall tension/wall area, and strain as the change in inner perimeter/inner perimeter at 10% capacity. The study showed a flat tracing from a traditional vesical pressure catheter during filling, but wall stress increased linearly, and compliance decreased exponentially. The next steps will need to see if these parameters can contribute to diagnosing voiding dysfunction and/or influence treatments of bladder dysfunction.

Many prior studies have not shown any negative impact of radiation on outcomes after artificial urinary sphincter implantation. Kaufman and coworkers¹⁰⁶ presented work on a multicenter analysis of idiopathic artificial urinary sphincter erosion ($n = 56$). The erosion-free median surgical survival without radiation was 3.15 versus 1.00 years with radiation ($P = .0327$), data that may be useful for counseling patients prior to implantation.

Finally, an exciting animal study shows the potential restorative function of electrical stimulation. Jiang and colleagues¹⁰⁷ presented work in the abstract “Long-term Pudendal Nerve Electrical Stimulation Accelerates Recovery From Stress Incontinence via Increased Neurotrophin Expression and Nerve Regeneration in an Animal Model.” The study used a simulated birth injury vaginal distension and pudendal nerve crush in rats, followed by electrical stimulation

versus sham stimulation of the pudendal nerve immediately after. Electrical stimulation significantly increased brain-derived neurotrophic factor and β II-tubulin expression in Onuf nucleus, demonstrating an increased neuroregenerative response. Clinically, leak point pressure and baseline external urinary sphincter electromyography amplitude increase after active treatment. If these findings translate to human birth injury, electrical stimulation could be considered to shorten postpartum stress urinary incontinence duration. The role of nerve stimulation could also be investigated to understand if it would prevent women undergoing vaginal delivery from developing incontinence later in life. ■

[Benjamin M. Brucker, MD]

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